

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

19.02.2004

Applicant's or agent's file reference
2003946-0022(VD1207)

IMPORTANT NOTIFICATION

International application No.
PCT/US 02/40744

International filing date (day/month/year)
18.12.2002

Priority date (day/month/year)
28.12.2001

Applicant
EISAI CO. LTD. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:

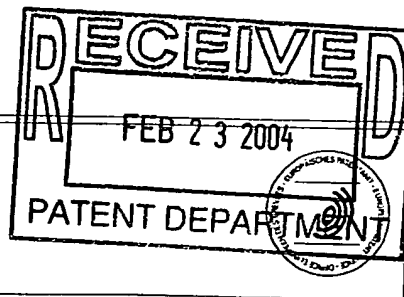


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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2003946-0022(VD1207)		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US 02/40744	International filing date (day/month/year) 18.12.2002	Priority date (day/month/year) 28.12.2001	
International Patent Classification (IPC) or both national classification and IPC C07D309/10			
Applicant EISAI CO. LTD. et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 9 sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the opinion</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p>			
Date of submission of the demand 25.07.2003		Date of completion of this report 19.02.2004	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Goss, I Telephone No. +49 89 2399-8292 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US 02/40744

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Claims, Numbers

1, 22-26, 43

received on 10.10.2003 with letter of 10.10.2003

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☒ the claims, Nos.: 44
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US 02/40744

☐ the entire international application,

☒ claims Nos. 43-64

because:

☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-64
	No: Claims	
Inventive step (IS)	Yes: Claims	1-64
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-42
	No: Claims	43-64

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 43 to 64 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Amendments

The recitation of the variable R7 in the proviso (i.e. "R₇ is hydrogen") is considered to be allowable as being considered as an obvious omission. The proviso introduced to specifically exclude the synthetic intermediates disclosed in D4 is also allowed as well as the correction to the structure given in claims 23 to 26 (namely the replacement of "OR5" with "R5").

Novelty

The present application relates to the development of synthetic methodologies enabling access to luminacin analogs having a broad range of biological and pharmacological activities.

The family of capillary tube formation inhibitors, designated luminacins, is now completely excluded at the end of both independent claims 1 and 22.

Novelty can be therefore recognized.

inventive step

The field of angiogenesis inhibitors, as also summarized by the applicant in the description, has vast applications in the provision of medicaments for the treatment of many diseases such as cancer. In view of the need for the development of further therapeutic agents useful for treating disorders that involve angiogenic activity, the problem underlying the present application can be seen in the provision of further luminacin analogs via synthetic methodologies.

Independent claims 1 and 22 refer to the compound claim and to the pharmaceutical composition containing them respectively and represent the solution to the problem

stated above.

D1 and D2 only refer to the natural compounds, isolated from the fermentation broth of an actinomycete strain, whereas D3 and in particular D4 both describe synthetic methods.

D3 on page 2069, right-hand column expressly teaches the fact that "src kinase activity is significantly up regulated in human cancers, particularly colon and breast cancers indicating the widespread role of src in human diseases".

D4 refers to the first total synthesis and establishment of absolute structure of luminacins C₁ and C₂ (which are the only luminacin compounds synthesised).

Therefore, the skilled man in the art faced with the problem of providing further derivatives/analogs via synthetic synthesis, knowing the teaching of D4, would only have taken an incentive to arrive at structurally similar natural products due to the very little synthetic variation suggested.

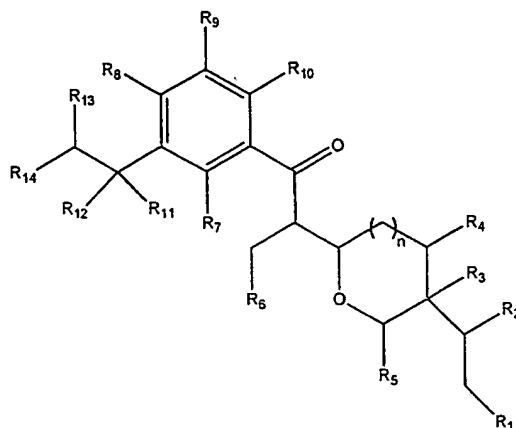
The compounds presently claimed are indeed structurally diverse lumicacin analogs so that an inventive step can be recognized.

Industrial applicability

For the assessment of the present claims 43 to 64 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims

1. A compound having the structure:



and pharmaceutically acceptable derivatives thereof;

wherein n is 0, 1 or 2;

R₁ is hydrogen or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R₂ and R₃ are each independently hydrogen, or, when taken together, may be -O- or -
(CH₂)_q-, wherein q is 1, 2 or 3;

R₄ is hydrogen, hydroxyl, protected hydroxyl or ORⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱ is an aliphatic or heteroaliphatic moiety;

R₅ is hydrogen, hydroxyl, protected hydroxyl or ORⁱⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱⁱ is an aliphatic or heteroaliphatic moiety, or wherein R₁ and R₅, when taken together, may form a cycloaliphatic or heterocycloaliphatic moiety comprising 6 to 12 atoms;

R₆ is hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R₇ is hydrogen, hydroxyl, protected hydroxyl, ORⁱⁱⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱⁱⁱ is an aliphatic or heteroaliphatic moiety;

R₈ is hydrogen, hydroxyl, protected hydroxyl or OR^{iv},

wherein R^{iv} is an aliphatic or heteroaliphatic moiety;

R₉ is hydrogen, -CF₃, -CHO, imine, hydrazone, oxime, carboxylic acid, carboxylic ester, acyl halide, ketone, amide, acetal, anhydride, dihalide, epoxide, nitrile or an aliphatic or heteroaliphatic moiety;

R₁₀ is hydroxyl or protected hydroxyl;

R₁₁ and R₁₂ are each independently hydrogen, hydroxyl or OR^y, or an aliphatic or heteroaliphatic moiety, or, when taken together, may be -(C=O)-;

wherein R^y is an aliphatic or heteroaliphatic moiety;

and R₁₃ and R₁₄ are each independently hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched, and whereby each of the foregoing aryl and heteroaryl moieties may be substituted or unsubstituted;

with the proviso that when R₄, R₅, R₈ and R₁₀ are each hydroxyl, R₁₃ and R₁₄ are each methyl, R₂ and R₃, taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:

R₁ is methyl, R₉ is hydrogen, (R₁₁, R₁₂) is (=O) and R₆ is ethyl or isopropyl;

R₁ is methyl, R₉ is CHO, (R₁₁, R₁₂) is (OMe, H) and R₆ is ethyl, propyl or isopropyl;

R₁ is methyl, R₉ is CHO, R₁₁ and R₁₂ are hydrogen and R₆ is ethyl, propyl or isopropyl;

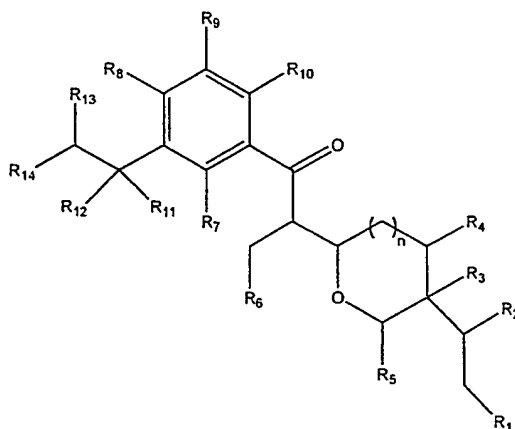
R₁ is methyl, R₉ is COCH₃, R₁₁ and R₁₂ are hydrogen and R₆ is ethyl; and

R₁ is ethyl, R₉ is CHO, R₁₁ and R₁₂ are hydrogen and R₆ is ethyl.

2. The compound of claim 1 wherein n is 1 and the compound has the structure:

substituted or unsubstituted, branched or unbranched or cyclic or acyclic, and wherein the aryl substituent may be substituted or unsubstituted.

20. The compound of claim 4 or 7 wherein R_{13} is lower alkyl, and wherein the alkyl substituent may be substituted or unsubstituted, linear or branched or cyclic or acyclic.
21. The compound of claim 7 wherein R_1 is hydrogen or lower alkyl, R_5 is hydroxyl or lower alkoxy, R_6 is lower alkyl, R_7 is hydrogen, hydroxyl, lower alkyl or lower alkoxy, R_8 is hydrogen, hydroxyl or protected hydroxyl, R_9 is $-\text{CHO}$ or $-\text{CH}_2\text{OR}^{\text{vi}}$, R_{11} and R_{12} are independently hydrogen or lower alkoxy, and R_{13} is lower alkyl; wherein R^{vi} is hydrogen, protecting group or an aliphatic or heteroaliphatic moiety; whereby each of the foregoing alkyl, alkoxy, aliphatic and heteroaliphatic moieties may be independently substituted or unsubstituted, linear or branched, or cyclic or acyclic.
22. A pharmaceutical composition comprising:
a compound having the structure:



and pharmaceutically acceptable derivatives thereof; and

a pharmaceutically acceptable carrier;

wherein n is 0, 1 or 2;

R_1 is hydrogen or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R₂ and R₃ are each independently hydrogen, or, when taken together, may be -O- or -(CH₂)_q-, where q is 1, 2 or 3;

R₄ is hydrogen, hydroxyl, protected hydroxyl or ORⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱ is an aliphatic or heteroaliphatic moiety;

R₅ is hydrogen, hydroxyl, protected hydroxyl or ORⁱⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱⁱ is an aliphatic or heteroaliphatic moiety, or wherein R₁ and R₅, when taken together, may form a cycloaliphatic or heterocycloaliphatic moiety comprising 6 to 12 atoms;

R₆ is hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R₇ is hydrogen, hydroxyl, protected hydroxyl, ORⁱⁱⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱⁱⁱ is an aliphatic or heteroaliphatic moiety;

R₈ is hydrogen, hydroxyl, protected hydroxyl or OR^{iv},

wherein R^{iv} is an aliphatic or heteroaliphatic moiety;

R₉ is hydrogen, -CF₃, -CHO, imine, hydrazone, oxime, carboxylic acid, carboxylic ester, acyl halide, ketone, amide, acetal, anhydride, dihalide, epoxide, nitrile or an aliphatic or heteroaliphatic moiety;

R₁₀ is hydroxyl or protected hydroxyl;

R₁₁ and R₁₂ are each independently hydrogen, hydroxyl or OR^v, or an aliphatic or heteroaliphatic moiety, or, when taken together, may be -(C=O)-;

wherein R^v is an aliphatic or heteroaliphatic moiety;

and R₁₃ and R₁₄ are each independently hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety; and

pharmaceutically acceptable derivatives thereof;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched, and whereby each of the foregoing aryl and heteroaryl moieties may be substituted or unsubstituted;

with the proviso that when R₄, R₅, R₈ and R₁₀ are each hydroxyl, R₁₃ and R₁₄ are each methyl, R₂ and R₃, taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:

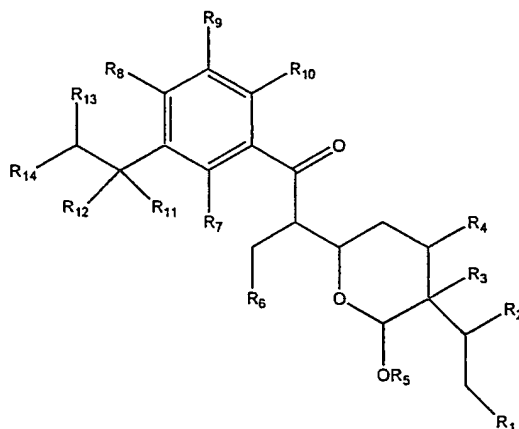
R₁ is methyl, R₉ is hydrogen, (R₁₁, R₁₂) is (=O) and R₆ is ethyl or isopropyl;

R_1 is methyl, R_9 is CHO, (R_{11} , R_{12}) is (OMe, H) and R_6 is ethyl, propyl or isopropyl;
 R_1 is methyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl, propyl or isopropyl;

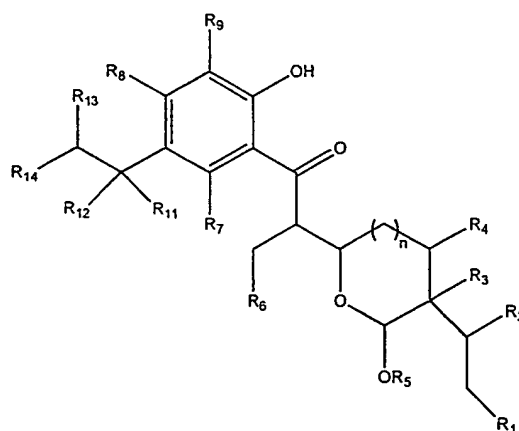
R_1 is methyl, R_9 is COCH₃, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and

R_1 is ethyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl.

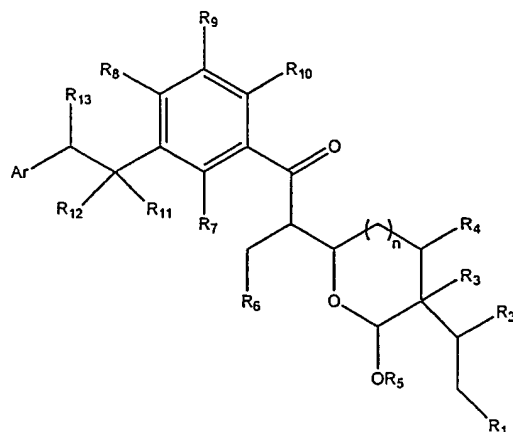
23. The pharmaceutical composition of claim 22 wherein n is 1 and the compound has the structure:



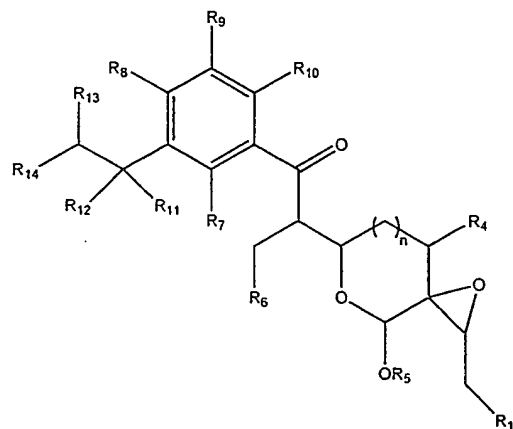
24. The pharmaceutical composition of claim 22 wherein R_{10} is hydroxyl and the compound has the structure:



25. The pharmaceutical composition of claim 22 wherein R_{14} is aryl and the compound has the structure:



26. The pharmaceutical composition of claim 22 wherein R_2 and R_3 , taken together, form an epoxide, and the compound has the structure:



27. The pharmaceutical composition of claim 22 wherein R_4 is hydroxyl and the compound has the structure:

44. The method of claim 43 wherein in the compound, when R_4 , R_5 , R_8 and R_{10} are each hydroxyl, R_{13} and R_{14} are each methyl, R_2 and R_3 , taken together, form an epoxide, and n is 1, the following groups do not occur simultaneously as defined:

R_1 is methyl, R_9 is hydrogen, (R_{11}, R_{12}) is $(=O)$ and R_6 is ethyl or isopropyl;

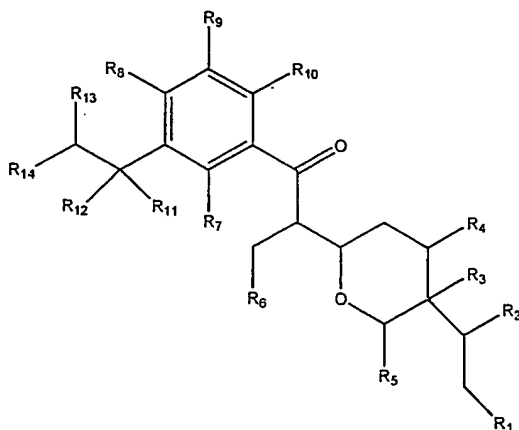
R_1 is methyl, R_9 is CHO, (R_{11}, R_{12}) is (OMe, H) and R_6 is ethyl, propyl or isopropyl;

R_1 is methyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl, propyl or isopropyl;

R_1 is methyl, R_9 is COCH₃, R_{11} and R_{12} are hydrogen and R_6 is ethyl; and

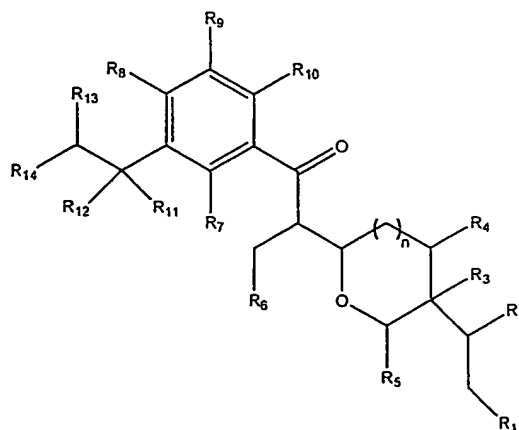
R_1 is ethyl, R_9 is CHO, R_{11} and R_{12} are hydrogen and R_6 is ethyl.

45. The method of claim 43 wherein in the compound n is 1 and the compound has the structure:



46. The method of claim 43 wherein in the compound R_{10} is hydroxyl and the compound has the structure:

40. The pharmaceutical composition of any one of claims 22, 23, 24, 26 or 27 wherein R_{13} and R_{14} are independently hydrogen, lower alkyl or aryl, wherein the alkyl substituent may be substituted or unsubstituted, branched or unbranched or cyclic or acyclic, and wherein the aryl substituent may be substituted or unsubstituted.
41. The pharmaceutical composition of claim 25 or 28 wherein R_{13} is lower alkyl, and wherein the alkyl substituent may be substituted or unsubstituted, linear or branched or cyclic or acyclic.
42. The pharmaceutical composition of claim 28 wherein R_1 is hydrogen or lower alkyl, R_5 is hydroxyl or lower alkoxy, R_6 is lower alkyl, R_7 is hydrogen, hydroxyl, lower alkyl or lower alkoxy, R_8 is hydrogen, hydroxyl or protected hydroxyl, R_9 is $-\text{CHO}$ or $-\text{CH}_2\text{OR}^{\text{vi}}$, R_{11} and R_{12} are independently hydrogen or lower alkoxy, and R_{13} is lower alkyl; wherein R^{vi} is hydrogen, protecting group or an aliphatic or heteroaliphatic moiety;
whereby each of the foregoing alkyl, alkoxy, aliphatic and heteroaliphatic moieties may be independently substituted or unsubstituted, linear or branched, or cyclic or acyclic.
43. A method for treating cancer comprising:
administering to a subject in need thereof a therapeutically effective amount of a compound having the structure:



and pharmaceutically acceptable derivatives thereof;

wherein n is 0, 1 or 2;

R₁ is hydrogen or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R₂ and R₃ are each independently hydrogen, or, when taken together, may be -O- or -(CH₂)_q-, where q is 1, 2 or 3;

R₄ is hydrogen, hydroxyl, protected hydroxyl or ORⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱ is an aliphatic or heteroaliphatic moiety;

R₅ is hydrogen, hydroxyl, protected hydroxyl or ORⁱⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱⁱ is an aliphatic or heteroaliphatic moiety, or wherein R₁ and R₅, when taken together, may form a cycloaliphatic or heterocycloaliphatic moiety comprising 6 to 12 atoms;

R₆ is hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

R₇ is hydrogen, hydroxyl, protected hydroxyl, ORⁱⁱⁱ, or an aliphatic or heteroaliphatic moiety,

wherein Rⁱⁱⁱ is an aliphatic or heteroaliphatic moiety;

R₈ is hydrogen, hydroxyl, protected hydroxyl or OR^{iv},

wherein R^{iv} is an aliphatic or heteroaliphatic moiety;

R₉ is hydrogen, -CF₃, -CHO, imine, hydrazone, oxime, carboxylic acid, carboxylic ester, acyl halide, ketone, amide, acetal, anhydride, dihalide, epoxide, nitrile or an aliphatic or heteroaliphatic moiety;

R₁₀ is hydroxyl or protected hydroxyl;

R₁₁ and R₁₂ are each independently hydrogen, hydroxyl or OR^v, or an aliphatic or heteroaliphatic moiety, or, when taken together, may be -(C=O)-;

wherein R^v is an aliphatic or heteroaliphatic moiety;

and R₁₃ and R₁₄ are each independently hydrogen, or an aliphatic, heteroaliphatic, aryl or heteroaryl moiety;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, linear or branched, and whereby each of the foregoing aryl and heteroaryl moieties may be substituted or unsubstituted.